ORIGINAL ARTICLE

Non-pegylated liposomal doxorubicin in lymphoma: patterns of toxicity and outcome in a large observational trial

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Abstract The anthracycline doxorubicin plays a major role in the treatment of lymphoproliferative disorders. However, its use is often limited due to cardiac toxicity, which seems to be much less in the liposomal non-pegylated formulation (Myocet®). The aim of this study was the evaluation of efficacy and toxicity of Myocet®-containing treatment regimens, with a focus on cardiotoxicity during treatment in lymphoma patients. A total of 326 consecutive patients, treated between March 2008 and December 2013 in 11 Austrian and 1 Italian cancer centers, were retrospectively assessed. Patients' baseline and treatment-related parameters were obtained by reviewing hospital records. Median age was 74 years (range 26–93). The most common histology was DLBCL (60 %), followed by FL (13 %) and MCL (8 %). At least one cardiovascular comorbidity was present in 72 % of patients. Most common grade 3/4 toxicities were hematologic, namely, leukopenia, neutropenia, thrombocytopenia, and febrile neutropenia in 44, 40, 17, and 16 %. Overall, 43 patients suffered a cardiac event (any grade) with most patients developing congestive heart failure. Parameters significantly associated with severe cardiac events (grades 3–5) were the presence of cardiovascular comorbidities, chronic obstructive pulmonary disease, and elevated baseline NT-proBNP. Treatment response after first line Myocet®-containing therapy was ≥58 % among all entities (range 58–86 %) and therefore comparable to those of conventional therapeutic regimens. Herein, we provide a detailed toxicity profile of Myocet®-containing chemotherapy regimens. Despite the high rate of patients with preexisting comorbidities, the number of adverse events was encouraging. However, these results need to be confirmed in a prospective randomized trial.

Keywords Anthracycline · Cardiac toxicity · Lymphoma · Myocet · R-CHOP

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Introduction

Non-Hodgkin's lymphoma (NHL) is the most common lymphoproliferative disorder. Since anthracyclines became available in 1969 with doxorubicin, the prognosis of many lymphomas has dramatically improved, especially when added to polychemotherapy regimens such as cyclophosphamide, vincristine and prednisolone (CHOP), and its variants (CHOP-like) [1]. However, especially in elderly patients, the use of doxorubicin is often limited due to anthracycline-induced cardiac toxicity [2–4]. These side effects often require dose reductions, treatment delays, or even omission of the anthracycline, leading to a dismal outcome [5]. Consequently, less toxic and equally potent options are needed.

Alternative formulations of doxorubicin, such as non-pegylated liposomal doxorubicin (Myocet®), with less cardiac side effects but preserved efficacy could represent an interesting alternative. Indeed, there is evidence that the ejection fraction, as a surrogate parameter for cardiac performance, is not affected by the administration of Myocet® [6–11]. A randomized controlled trial in patients affected by metastatic breast cancer showed comparable efficacy with less cardiac events when comparing Myocet® with doxorubicin (13 vs 29 %) [8]. Hence, Myocet® has also been administered off-label to many lymphoma and myeloma patients as a less toxic alternative to doxorubicin. Also, according to the guidelines of the European Society for Medical Oncology, substitution of doxorubicin by liposomal doxorubicin is recommended for patients with cardiac dysfunction or who are otherwise unfit [12]. Preliminary data regarding efficacy and toxicity in elderly patients with poor risk DLBCL showed a high response rate after the combination of rituximab, cyclophosphamide, Myocet®, and prednisone (R-COMP) with only a few treatment-related cardiac events [10, 11]. Even in patients with preexisting cardiac disorders, favorable results were observed [13]. However, real-live data of large patient cohorts assessing the efficacy and tolerability of Myocet®-containing treatment regimens is lacking. Therefore, we performed the so far largest multicenter observational study evaluating the spectrum and frequency of side effects and the efficacy of Myocet®-based chemotherapy in a real-life setting.

Patients and methods

Patients

Eleven Austrian and one Italian cancer center retrospectively assessed all patients affected by a lymphoproliferative disease, who underwent a Myocet®-based treatment between March 2008 and December 2013. This resulted in a cohort of 326 consecutive, unselected patients. Patients' characteristics at diagnosis (Table 1), chemotherapy details, toxicities (Tables 2

and 3, Supplementary Table 1), and outcome (Table 4, Figs. 1 and 2) were registered. Follow-up data was obtained from hospital files and primary physicians. The final data update was performed in January 2014. This study was approved by the Ethics Committee of the Medical University of Innsbruck.

Treatment

All patients who received at least one Myocet®-containing therapy and met the above-mentioned criteria were included into this analysis. Most patients underwent R-COMP (cyclophosphamide 750 mg/m^2, vincristine 2 mg, Myocet® 50 mg/m^2, prednisone 40 mg/m^2, and rituximab 375 mg/m^2; n=287). 19 T-NHL patients received COMP without rituximab. While a curative approach was intended in all cases, dose modifications, treatment delays, switches to another treatment regimen, and premature treatment termination were often necessary. Other treatment regimens containing Myocet® were the following: alemtuzumab plus COMP (three patients); bortezomib plus COMP (one patient); cyclophosphamide, vincristin, procarbazine, prednisone alternating with Myocet®, bleomycin, vinblastine, and dacarbazine (COPP-MBVD, one patient); ofatumumab plus COMP (one patient); bortezomib, Myocet®, and dexamethasone (ten patients); and cyclophosphamide, navelbine, Myocet®, prednisone (four patients). In accordance with the European Organisation for Research and Treatment of Cancer guidelines [14], granulocyte colony-stimulating factor (G-CSF) support was given in most cases.

Evaluation of toxicity

Toxicities, documented within the time interval between administration of first Myocet® dose and 2 months after the last dose of the respective therapy line, were graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE, version 4.0). Cardiotoxicity was documented during Myocet®-based therapy and at any time point thereafter. In order to better distinguish early from late onset cardiotoxicity, we categorized whether cardiotoxicity was experienced "during Myocet®-based therapy" (including the time interval of 2 months after last dose) or in the subsequent period (Table 3, Supplementary Table 1). To identify possible risk factors, the association of baseline characteristics and laboratory parameters with all cardiac events and cardiac events of grades 3–5 was analyzed. The following parameters were evaluated: sex, age (<60 vs ≥60 years), histology, stage of disease, performance status (ECOG ≤1 vs ≥2), presence or absence of B symptoms, international prognostic index (IPI), and co-morbidities at times of diagnosis such as cardiovascular diseases, diabetes, chronic obstructive pulmonary disease (COPD), gastrointestinal disorders, rheumatic diseases,

Table 1 Patients' characteristics at time of start of Myocet-based therapy

	N	Valid	%
Age, median (range)	74 (26–93)	326	
Age >70 years	219	326	67
Male	189	326	58
B symptoms	153	309	50
Performance status ≥2	90	314	29
LDH>UNL	159	310	51
≥2 Extranodal sites involved	90	282	32
Stage 3/4 in NHL	217	308	70
Histology¥		326	
DLBCL	194		60
FL GIII	25		8
MCL	24		7
Peripheral T-NHL	19		6
FL GI/II	17		5
CLL/Richter's	15		5
Myeloma	11		3
Marginal zone/MALT	9		3
CLL	7		2
Other±	5		2
IPI risk factors (aggressive NHL)*		200	
0-I	39		19
II	43		21
III	58		29
IV	46		23
V	14		7
Anemia (hemoglobin<12 g/dL)	132	278	48
Thrombocytopenia (PLT<150 G/L)	51	258	20
C-reactive protein (≥1mg/dl)	138	260	53
B2MG >UNL	106	121	88
Troponin T >UNL	21	48	44
BNP >UNL	69	95	73
LVEF median (range)	60 (27-90)	169	
Preexisting comorbidities		326	
Cardiovascular diseases	236		72
Diabetes mellitus	54		17
Prior/concomitant neoplasias	67		21
Gastrointestinal disorders	52		16
Renal impairment (creatinine 1.3 mmol/l)	55		17
Neurological disorders	56		7
Lung diseases	43		13
Psychiatric disorders	11		3
Prior therapy		326	
Chemotherapy**	70		21
Radiotherapy	22		7

BNP brain natriuretic peptide, *UNL* upper normal limit, *LVEF* left ventricular ejection fraction, *B2MG* beta-2-microglobulin, *LDH* lactate dehydrogenase, *IPI* international prognostic index, *FLIPI* follicular lymphoma international prognostic index, *MIPI* mantle cell lymphoma international prognostic index

± Burkitt/Burkitt-like (2); macroglobulinemia Waldenstrom (2); Hodgkin's lymphoma (1)

¥ Number of patients with Myocet-based therapy in respective line (first/higher): DLBCL, 166/28; FL grade III, 21/4; FL grades I/II, 14/3; MCL, 18/6; peripheral T-NHL, 19/0; CLL, 1/6; other lymphoma type, 23/17

*Including DLBCL and T-NHL

**Prior line of chemotherapy, not containing Myocet

renal impairment, impaired cardiac function (ejection fraction [LVEF] <55 %), and prior cancers with or without prior antitumor therapies. Moreover, the following laboratory parameters were evaluated: hemoglobin level, count of leukocytes, neutrophils and thrombocytes, troponin T, NT-proBNP, C-reactive protein.

Table 2 Toxicity during (and within 2 months after) Myocet®-containing polychemotherapy according to the CTC grades

		Total	Valid	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Deaths (%)
Hematologic toxicity	Leukopenia	202	326	29 (9)	31 (10)	47 (14)	95 (29)	0
	Neutropenia	159	326	8 (3)	20 (6)	26 (8)	105 (32)	0
	Anemia	175	326	46 (14)	74 (23)	36 (11)	19 (6)	0
	Thrombopenia	103	326	29 (9)	19 (6)	21 (6)	34 (10)	0
	Febrile neutropenia	51	326	–	–	–	51 (16)	7 (2)
Non-hematologic toxicity	Parasthesia	55	326	19 (6)	33 (10)	2 (<1)	1 (<1)	0
	Gastrointestinal	30	326	13 (4)	5 (2)	4 (1)	7 (2)	1 (<1)
	Infections	135	326	16 (5)	26 (8)	24 (7)	57 (18)	12 (4)
	Cardiac	43	326	7 (2)	13 (4)	4 (1)	12 (4)	7 (2)

Evaluation of response and survival

Complete remission (CR) and partial remission (PR) were assessed according to the disease-specific response criteria [15–18]. In all cases, response had to persist for at least 2 months. Progression-free survival (PFS) was measured from first day of the Myocet®-based therapy to disease progression or death, whatever occurred first, and overall survival (OS) was measured from initiation of Myocet® therapy to last follow-up or death of any cause.

Statistical analyses

Chi-square test was performed to assess the significance of differences between categorical variables. The significance of distribution differences between subgroups was assessed with the Mann–Whitney U test. PFS and OS were plotted as a curve using the Kaplan–Meier method. Log-rank test was employed to assess the impact of categorical variables on survival. A P value of <0.05 was considered as statistically significant. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) software v.17.0.1 (SPSS, Chicago, IL, USA).

Results

Patient characteristics at start of Myocet®-based therapy

Patient characteristics at start of Myocet®-based therapy are summarized in Table 1. Overall, most patients were of advanced age (median 74 years, range 26–93 years) and of male gender (58 %). Only the minority had a poor performance status (90/314 informative cases, 29 %). The most common lymphoproliferative disorder was DLBCL (n=194; 60 %), followed by FL grade 3 (25; 8 %), MCL (24; 7 %), peripheral T-NHL (19; 6 %), and other lymphoma entities. Most patients presented with advanced stage of disease and adverse prognosticators (Table 1).

Table 3 Type of cardiac event of any grade during and after Myocet-based therapy

Cardiac event	During treatment N	Valid	%	After treatment N (%)	Valid*	%
Arrhythmia	15**	326	5	5**	274	2
Instable angina pectoris	4		1	2		0.7
ACS/MCI	12		4	3		1
CHF	27		8	13		5
SCD	2		0.6	2		0.7
Blood pressure dysregulation***	3		0.9	0		0

Cave one patient may have suffered from >1 cardiac event, *ACS* acute coronary syndrome, *MCI* myocardial infarction, *CHF* congestive heart failure, *SCD* sudden cardiac death

*In patients who survived at least 2 months after last dose of Myocet

**During treatment: atrial fibrillation (*n*=11), arrhythmia not otherwise specified (3); atrioventricular block (1); after treatment: atrial fibrillation (5)

***Orthostatic dysregulation (*n*=2); hypertensive emergency (1)

Table 4 Response and relapse according to the histological subgroup

	ORR		CR		PR		SD		PD		Treatment not completed		Death during therapy		Relapse	
Histological entity	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
DLBCL 1st line	124	75	100	60	24	14	3	2	13	8	14	8	11	7	19	11
FL G III 1st line	17	81	15	71	2	10	1	5	1	5	1	5	1	5	4	19
FL G I/II 1st line	12	86	10	71	2	14	0	0	0	0	1	7	1	7	0	0
MCL 1st line	14	78	12	67	2	11	1	6	1	6	1	6	0	0	4	22
T-NHL 1st line	11	58	6	32	5	26	0	0	6	32	0	0	2	11	4	21

Treatment

Overall, the median cumulative Myocet® dose was 225 mg/m² (20–400 mg/m²), and the median number of chemotherapy cycles containing Myocet® was 5 (range 1–8 cycles). In detail, in first line therapy, a median of 6 cycles of Myocet®-containing chemotherapy was administered (range 1–8) with an overall median cumulative dose of 240 mg/m² (range 20–400 mg/m²). Seventy patients (21 %) received previous chemotherapy while 22 (7 %) were pretreated with radiotherapy (RT). In patients treated in higher lines, number of cycles (median 4, range 1–6) and cumulative Myocet® doses (150 mg/m², 37.5–300 mg/m²) were significantly lower compared to the first line therapy ($P<0.001$ for each comparison). There was no difference in numbers of cycles and cumulative dose in the different tumor entities, both in the first and higher line setting, respectively. In 21/326 patients (6 %), a switch from doxorubicin to Myocet® within a treatment line (after a median of 3 cycles, range 1–5 cycles) was performed. Of 1581 anthracycline-containing chemotherapies, 1494 contained Myocet® (95 %). RT within the same therapy line (mostly with intent of consolidation) was delivered to 31 patients (11 %).

Toxicity of Myocet®-based treatment

Hematologic and extrahematologic toxicities during Myocet®-based therapy and within 2 months after last dose, according to the CTC grades, are detailed in Table 2. As expected, the most common grade 3/4 toxicities were hematologic consisting mainly of leukopenia, neutropenia, thrombocytopenia, as well as febrile neutropenia in 142/326 (44 %), 131/326 (40 %), 55/326 (17 %), and 51/326 cases (16 %), respectively. Severe hematologic toxicities, including febrile neutropenia, were significantly more often observed in patients who had undergone a previous treatment line (neutropenia, 58 vs 36 %, $P=0.001$; thrombocytopenia, 39 vs 12 %, $P<0.001$; febrile neutropenia, 25 vs 13 %, $P=0.022$). Non-hematologic toxicities were less frequent, but more often led to fatal events ($n=20$).
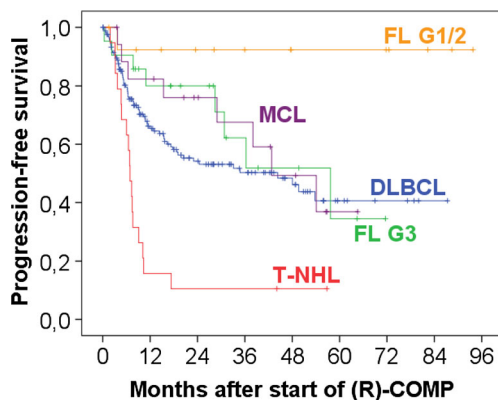

Fig. 1 This Kaplan–Meier plots illustrates progression-free survival (PFS) in five different lymphoma entities treated *in first line* with R-COMP (or COMP regimen in T-NHL). The median PFS and 3-year PFS were 44.3 months and 50 % in DLBCL ($n=166$), respectively; 57.7 months and 62 % in follicular lymphoma grade 3 (FL G3, $n=21$), respectively; not reached and 92 % in follicular lymphoma grades 1 and 2 respectively; 42.8 months and 68 % in mantle cell lymphoma (MCL, $n=18$), respectively; and 6.9 months and 11 % in peripheral T cell lymphoma (T-NHL, $n=19$)
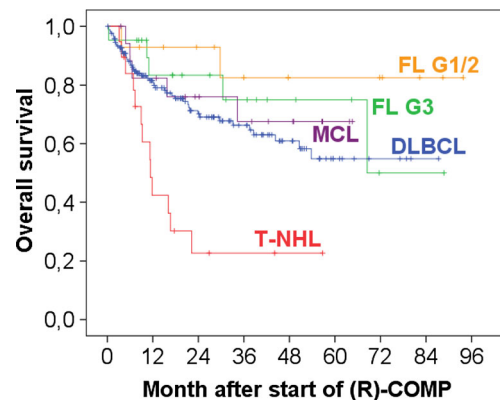

Fig. 2 This Kaplan–Meier plots illustrates overall survival (OS) in five different lymphoma entities treated *in first line* with R-COMP (or COMP regimen in T-NHL). The median OS and 3-year OS were not reached and 66 % in DLBCL ($n=166$), respectively; 68.5 months and 75 % in follicular lymphoma grade 3 (FL G3, $n=21$), respectively; not reached and 83 % in follicular lymphoma grades 1 and 2, respectively; not reached and 68 % in mantle cell lymphoma (MCL, $n=18$), respectively; and 11.3 months and 23 % in peripheral T cell lymphoma (T-NHL, $n=19$)

A major focus was set on the detailed analysis of cardiac events occurring during treatment period (after the first dose of Myocet® until 2 months after the last dose). In Supplementary Table 1, the most important characteristics of patients who suffered cardiac events during a Myocet®-based therapy are described, including long-term follow-up information. Briefly, in 43/326 patients (13 %) a cardiac event was documented within the above-mentioned time period. Four patients experienced grade 3 toxicities, namely, clinically manifest congestive heart failure, accompanied with acute coronary syndrome in two cases, and 12 patients suffered from grade 4 toxicities consisting of severe congestive heart failure in 10 cases, myocardial infarction in one, and arrhythmia accompanied with an atrioventricular block of grade 3 in one patient. Therapy-associated cardiac deaths were documented in seven patients of whom four experienced a myocardial infarction leading to fatal congestive heart failure, two a sudden cardiac arrest, and one a fatal congestive heart failure during first cycle of a Myocet®-based therapy. All therapy-associated events of any grade are summarized in Table 3.

Parameters associated with elevated incidence of cardiac adverse events irrespective of grade were the presence of COPD (in 33 vs 10 % in patients without COPD, $P<0.001$) and elevated NT-proBNP (20 vs 4 %, $P=0.05$). Parameters associated with severe cardiac toxicity (grades 3–5) were the presence of cardiovascular comorbidity (9 vs 2 %, $P=0.035$), COPD (19 vs 5 %, $P=0.002$), and elevated NT-proBNP (15 vs 0 %, $P=0.04$). The most homogeneous cohort in our observational trial was the group of DLBCL patients treated with R-COMP in first line ($n=149$). A comparison of this cohort to historical cohorts who received conventional doxorubicin has recently been published [19]. Of note, the proportion of cardiotoxicity and severe cardiotoxicty in this group (including cardiac deaths) was not different when compared to the rest of patients ($n=177$), who were characterized by varying patients' characteristics, were partly pretreated, and often received different Myocet-based regimens.

Finally, cardiac events occurring >2 months after the last dose of Myocet® were documented in 18 cases (6 %), as detailed in Supplementary Table 1 and Table 3. In three of these patients, cardiotoxicitiy was also observed during Myocet®-based therapy. However, it is likely that in a relevant number of patients, cardiac events in the time after Myocet®-based therapy were not documented due to less frequent hospital visits after completion of chemotherapeutic treatment. Thus, no further analyses were perfomed in this cohort.

Response upon Myocet®-based therapy

Treatment response upon a Myocet®-based first line therapy according to the different histologic subtypes is summarized in Table 4. High overall response rates (ORR) were observed among all entities and were comparable to those of conventional therapies (e.g. of (R)-CHOP).

Overall, a response was achieved in 226/326 patients (ORR 69 %). Response in first line and higher line of therapy was achieved in 76 and 47 %, respectively ($P<0.001$). Nonresponders had significantly more often an elevated LDH ($P<0.001$), poor performance status ($P<0.001$), LVEF< 50 % ($P=0.001$), elevated NT-proBNP ($P=0.014$), and thrombocytopenia <150 G/L ($P=0.028$) at time of treatment initiation.

Survival after start of Myocet®-based therapy

Survival analysis was performed in patients with Myocet®-based treatment in first line setting ($n=262$). PFS was calculated only for the major histologic entities, namely, DLBCL ($n=166$, 3 year PFS 50 %), FL grade 3 ($n=21$, 3-year PFS 62 %), peripheral T-NHL ($n=19$, 3-year PFS 11 %), MCL ($n=18$, 3-year PFS 68 %), and FL grades 1–2 ($n=14$, 3-year PFS 92 %) (Fig. 1). Apart from the type of lymphoproliferative disease, PFS was also negatively influenced by an elevated C-reactive protein ($P<0.001$), unfavorable IPI in the case of aggressive B cell NHL ($P<0.001$), low hemoglobin ($P<0.001$), presence of B symptoms ($P=0.005$), elevated ß$_2$-microglobuline ($P=0.023$), NT-proBNP ($P=0.029$) above the upper normal value, and LVEF<55 % ($P=0.047$).

OS, again calculated in patients with Myocet® in first line, varied according to the different entities, and 3-year OS was 66 % for DLBCL ($n=166$), 75 % for FL grade 3 ($n=21$), 23 % for peripheral T-NHL ($n=19$), 68 % for MCL ($n=18$), and 83 % for FL grades 1–2 ($n=14$) (Fig. 2). Survival was significantly influenced by an elevated C-reactive protein ($P<0.001$), low hemoglobin ($P<0.001$), unfavorable IPI in the case of aggressive B cell NHL ($P<0.001$), LVEF<55 % ($P=0.003$), elevated NT-proBNP ($P=0.011$), and the presence of B symptoms ($P=0.002$).

Discussion

In our previous work, we retrospectively showed that R-COMP as first line chemo-immune therapy in DLBCL is efficacious and well tolerated when compared with R-CHOP; together with the Austrian prospective phase II data by Fridrik et al. [19, 20], it is convincingly demonstrated that R-COMP is able to cure patients with DLBCL, and its potential is comparable with the standard R-CHOP regimen. The reason for substituting classic doxorubicin by Myocet® is mainly to protect the heart from doxorubicin-associated acute and long-term cardiotoxicity. Nevertheless, Myocet® is licensed in combination with cyclophosphamide in metastatic breast cancer, and two large phase III studies as well as one

meta-analysis evidenced that liposomal doxorubicin is less cardiotoxic than classic doxorubicin [7, 8]. Nevertheless, the authors of the meta-analysis concluded that the definitive recommendation in favor of liposomal formulations cannot be given so far [21]. On the other hand, the ESMO guidelines [12] suggest the substitution of doxorubicin with liposomal doxorubicin as option for patients with DLBCL and cardiac dysfunction. Apart from biological issues, several clinical questions still have to be answered: Can the favorable tolerability of Myocet® also be taken for granted in lymphoma? Should Myocet®-based therapy be reserved for the elderly and/or patients with preexisting cardiac comorbidities [22, 23]? Should it also be administered to the young patients facing a long lifetime after cure? Should Myocet® be given to all patients requiring a Doxorubicin-containing (immuno-) chemotherapy?

In this observational study, we put the focus on detailed analyses of toxicity and efficacy of Myocet®-based therapies in the so far largest cohort of patients affected by a hematologic neoplasia ($n=326$). This enabled us to provide detailed subgroup analyses. However, due to the retrospective nature and the lack of a direct comparison to analogous therapies using classic doxorubicin, it cannot definitely be stated whether a Myocet®-based therapy is less cardiotoxic or not.

The pattern of acute, non-severe, and severe cardiac events in the present analysis reflected the expected spectrum of adverse events of an anthracycline-based therapy, such as congestive heart failure, arrhythmia, acute coronary syndrome, and even sudden cardiac death. Indeed, the quantity of cardiac events appears significant in our study. Nevertheless, it must be considered that the present study population is highly selected for preexisting cardiac comorbidities, representing patients in whom administration of conventional doxorubicin would have been contraindicated. Indeed, this might be an explanation for the high percentage of cardiovascular events occurring during Myocet® treatment. Long-term cardiovascular events in our study probably are underreported due to the retrospective study design with a considerable proportion of patients lost to follow-up. Anyhow, such an analysis certainly should be performed prospectively and demands a long, closely monitored observational period [24].

Maybe the most important finding in this study is the identification of factors predicting the occurrence of cardiac events. Herein, for the first time, baseline clinical parameters associated with Myocet®-associated cardiotoxicity were identified. Of all evaluated factors, cardiac comorbidities of any kind, elevated NT-proBNP and preexisting COPD, appeared to represent a state of elevated risk for cardiotoxicity under Myocet®-based therapy. Unexpectedly, impaired LVEF at treatment start did not unambiguously predict cardiotoxicity, in line with the observation by Jurzak et al. [25]. Nevertheless, early decline in LVEF was reported to predict cardiotoxicity in lymphoma patients [26]. The remaining parameters

suggestive for a poor outcome, namely, increased age, poor performance status, anemia, and parameters indicative of advanced disease, such as high stage of disease or elevated LDH, did not favor the occurrence of cardiac events. Finally, cardiotoxicity was not increased in patients who were treated with a Myocet®-containing therapy in a higher line, i.e., after relapse in salvage therapy. Therefore, we recommend a complete cardiac workup including electrocardiography, echocardiography, spirometry, and determination of NT-proBNP before starting any kind of anthracycline-based therapy. Despite the herein reported favorable toxicity profile in patients with preexisting cardiac comorbidities, studies with a long-term follow-up to investigate whether this drug should be reserved to similar patients or if also others without such disorders might profit from Myocet® are urgently warranted. Indeed, data from breast cancer studies proved that liposomal doxorubicin is less cardiotoxic when compared prospectively to classic doxorubicin. Therefore, the use of Myocet®-based therapy would be of major importance in younger patients who have the chance of cure and an estimated rather long survival.

Other severe toxicities such as cytopenia, severe infections, and febrile neutropenia were frequent, but manageable in most cases. The number of adverse events was within the expected range, when compared to a phase II trial evaluating R-COMP in elderly DLBCL patients [27]. This observation certainly reflects the quality of our retrospective toxicity assessment.

Considering the accumulation of comorbidities in the presented cohort, response and cure rates are encouraging, suggesting that this treatment is a valid option for doxorubicin-unfit patients (Table 4; Figs. 1 and 2). Although this analysis was not powered to evaluate the response rate, the ORR of DLBCL patients after first line therapy was similar to the one reported by Luminari et al. [27] (ORR 71 % as compared to 75 % in our study) and others [19, 22]. However, PFS and OS seem slightly inferior in our cohort, certainly explained due to the inferior basic characteristics. Nevertheless, patients who received ≥300 mg/m^2 Myocet® had a 3-year OS close to 80 % (not shown in detail).

In conclusion, in this real-life patient setting, we characterized in detail the spectrum of cardiotoxicities which can occur during a Myocet®-based therapy in lymphoma, identified prognosticators for such events, and showed that these treatments offer a reasonable chance of cure. However, a definite superiority of Myocet® in terms of toxicity and/or efficacy can only be demonstrated in prospective trials comparing Myocet®-containing regimens to the actual standard of care for each entity.

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